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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. |
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| 09/068,377 | 05/08/99 | LASKY | L P1066P2 |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

**Commissioner of Patents and Trademarks**

| Office Action Summary | Application No. 09/068,377 | Applicant(s) LASKY ET AL. | |
|---|---|---|---|
| | Examiner Stephen L. Rawlings, Ph.D. | Art Unit 1642 | |

*-- The MAILING DATE of this communication appears on th c ver she t with the correspond nce address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *29 January 2001* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) *1-14 and 19-21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15-18 and 22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claims *1-22* are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☒ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. § 119**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

**Attachment(s)**

15) ☐ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *17* .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☒ Other: *Notice to Comply* .

## DETAILED ACTION

1. The Amendment filed on January 29, 2001 (Paper No. 16) is acknowledged and has been entered. Claims 15 and 22 have been amended.

2. Claims 1-22 are pending in the application. Claims 1-14 and 19-21 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention. Claims 15-18 and 22 are currently under prosecution.

3. The text of those sections of Title 35, U.S. Code not included in this Office Action can be found in the prior Office Action.

### *Priority*

4. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. § 119(e) as follows:

An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification (37 CFR 1.78). Applicant states that "no claim to the benefit of a provisional application was made" in the original filing on page 4 in paragraph 2 of the Response to the Office Action mailed on November 7, 2000. Nonetheless, it has been noted that the original and substitute declarations claim the benefit of the filing date of an application with serial no. 08/798,419 and furthermore, the specification, as amended in Paper No. 16, now reflects the fact that this claim of benefit is made in the first paragraph. The latter application, referred to in the declaration and specification, was converted by the Applicant to a provisional application, which has now been assigned the serial no. 60/104,589. It appears that at the time the original application was filed this conversion was pending, as evidenced by the original declaration. Because the conversion is not now pending and a serial number has been assigned to the converted, provisional application, the specification must be amended to contain a specific and proper reference to this prior application to receive the benefit of the earlier

filing date. If as Applicant stated, a claim to the benefit of the filing date of the provisional application under 35 USC § 119(e) is not made, then the specification must be amended to delete the claim that now appears in the first paragraph at page 4, line 4 and a substitute declaration is required, which does not claim benefit of the provisional application.

***Oath/Declaration***

5. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

It does not state that the person making the oath or declaration has reviewed and understands the contents of the specification, including the claims, as amended by any amendment specifically referred to in the oath or declaration.

Also, as was noted above, a substitute declaration with a proper claim to the benefit of the earlier filing date of the provisional application (serial no. 60/104,589) must be submitted, if it is so desired. Otherwise, a substitute declaration that does not claim the benefit of the filing date of application serial no. 08/798,419 under 35 USC § 119(e) must be submitted.

***Specification***

6. This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

It is noted that in the Response to the Office Action mailed on November 7, 2000, Applicant states that "a replacement sheet has been attached" (page 4, paragraph 5). However, the replacement sheet has not been located and appears not have been attached.

7. The specification must be amended to reflect the actual priority claimed that is being claimed.

***Sequence Listing Compliance***

8. The communication filed January 29, 2001 is not fully responsive to the Office communication mailed November 7, 2000 for the reason(s) set forth on the attached Notice To Comply With The Sequence Rules or CRF Diskette Problem Report. Applicant must comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825) before the application can be examined under 35 U.S.C. §§ 131 and 132.

Since the reply appears to be bona fide attempt to comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825), applicant is given the same time period within which to comply as is available to respond to this Office Action.

***Response to Arguments***

***Claim Rejections - 35 USC § 101***

9. Applicant's arguments filed January 29, 2001 have been fully considered and this rejection is withdrawn. In view of the fact that the utility of a PSTPIP polypeptide to which the claimed antibody specifically binds was determined to be patentable (US 6,111,073 A) and therefore to have a utility, the antibody claimed in the instant application must also have utility. The primary reason for the decision to withdraw this rejection is that in the Office Action mailed on November 7, 2001, the examiner stated, as was noted by Applicant in the Response (page 5), that "the utility of an antibody to a specific protein, such as PSTPIP, is dependent upon the utility of the protein to which it binds". While the other arguments set forth in the Response to the 35 USC §101 rejection are not found persuasive, clearly the issuance of a patent with claims for a polypeptide comprising SEQ ID NO: 1 is strong evidence that the Office has acknowledged the utility of this protein. However, it is noted that the scope of the claims in the instant application encompass a large genus of molecules that are perhaps only marginally related to the PSTPIP polypeptide comprising SEQ ID NO: 1 in structure and/or function. In the Office Action mailed November 7, 2000, the examiner cited several references that teach that the effects of amino acid substitutions in proteins

cannot be predicted by one of skill in the art without further experimentation. It is noted that in the Response to the Office Action, Applicant does not specifically refute the teachings of the prior art that were cited in the rejection. Also, Applicant does not provide any evidence that PSTPIP (SEQ ID NO: 1), or more particularly the claimed genus of PSTPIP-like molecules is capable of directly catalyzing actin polymerization. Thus, one of skill in the art cannot predict the utility of the genus of PSTPIP-like molecules that vary in sequence relative to the prototypal molecule comprising SEQ ID NO: 1. Because one cannot predict the utility of a PSTPIP-like molecule, one of skill in the art cannot predict the utility of an antibody capable of specific binding to the molecule. Furthermore, while it cannot be predicted that a PSTPIP-like molecule will have any activity, other than the ability to bind a protein tyrosine phosphatase (a limitation in the claims), certainly it cannot be predicted whether the antibody will be an agonist, an antagonist, or if its binding will have any effect upon the activity of the molecule. With regard to the asserted utility for an antibody capable of specific binding to a PSTPIP-like molecule in an assay to measure proliferating cells, which in the opinion of the examiner is non-specific, it cannot be predicted that each member of the genus of PSTPIP-like molecules encompassed by the claims will be expressed in a cell-cycle dependent manner. Therefore, one of skill in the art cannot predict whether each member of the claimed genus of antibodies capable of specific binding to each different member of the genus of PSTPIP-like molecules will be useful in such an assay. Therefore, the examiner does not acquiesce to the Applicant that there is a specific and substantial asserted utility for the genus of antibodies that specifically bind the multitude of PSTPIP-like molecules encompassed by the claims. However, since the standard held by the Office requires that an invention have only one specific and substantial or well-established asserted utility and in view of the fact that there is an acknowledged utility for a species of antibody capable of specific binding to the PSTPIP polypeptide comprising SEQ ID NO: 2 (US 6,111,073 A), the utility rejection is withdrawn.

***Claim Rejections - 35 USC § 112***

***First Paragraph***

10. Applicant's arguments filed January 29, 2001 have been fully considered but are not found to be persuasive and these rejections are maintained.

With regard to section 8 of the Office Action of November 7, 2000, Applicant argues that the issuance of US 6,111,073 A provides sufficient evidence that an antibody capable of specific binding to a PSTPIP polypeptide is supported by an asserted utility; this point is made in view of the examiner's statement in the Office Action that the utility of the claimed antibody depends upon the utility of the polypeptide to which it binds. Since it is clear that the Office has determined that there is at least one asserted utility for the PSTPIP polypeptide comprising the amino acid sequence set forth in SEQ ID NO: 1, as evidenced by US 6,111,073 A, the 35 USC § 101 rejection has been withdrawn (as indicated above). However, the grounds for the 35 USC § 112, first paragraph rejection in section 8 of the Office Action are still considered to be tenable, because different standards are used by the Office to determine whether one of skill in the art can make and/or use the invention.

Again, the standard used by the Office in determining whether an invention is supported by an asserted utility does not require that every aspect of the invention encompassed by the breadth of the claims have utility; rather, it is only necessary that at least one asserted utility for at least one aspect of the invention be found to be either specific and substantial or well-established. On the other hand, the standard used by the Office in determining whether the specification is enabling is different, requiring that the invention, as drawn to the full scope of the claims, be supported by either a specific and substantial or a well-established asserted utility.

In this instance, the examiner stated that "it is impossible to establish a specific and substantial asserted utility for amino acid sequence variants or other mammalian homologues of mouse PSTPIP [SEQ ID NO: 1], since the specific biological function of said variants and homologues can not be predicted based upon sequence similarity alone" (page 8). The examiner also stated that "in the absence of evidence of any

specific biological function, for example that PSTPIP is able to induce the polymerization of actin monomers in isolation of other components of the regulatory cascade, one of skill in the art cannot predict that a PSTPIP polypeptide will have the ability to do so (page 6). However, it is noted that Applicant does not refute the fact that the effects of sequence alterations upon the function of protein variants are unpredictable.

Applicant argues that "the demonstration of a specific activity is sufficient to demonstrate utility without a demonstration of an exact mechanism" (page 5, paragraph 4). However, the only specific activities that are demonstrated in the specification are the ability of the PSTPIP polypeptide comprising SEQ ID NO: 1 to bind to PTP HCSF, a protein tyrosine phosphatase (Example I, pages 38-40 of the specification), and the ability of the polypeptide to act as a substrate for this phosphatase (Example III, pages 41-42). Although, according to Applicant, the asserted utility for PSTPIP and protein variants thereof is to induce polymerization of actin monomers (page 34, lines 38-39 of the specification), a *specific* activity of PSTPIP that has not been proven. Moreover, there is no exemplification in the specification that demonstrates any specific activity of a variant of this PSTPIP polypeptide. Then, according to Applicant's statement above, there is insufficient evidence of utility for these PSTPIP-like polypeptide variants and so the argument is not found to be persuasive. Certainly without any knowledge of the specific activity of these PSTPIP-like polypeptide variants, one of skill in the art cannot predict whether an antibody capable of specific binding to a variant will be an agonist or an antagonist of this undisclosed and unpredictable activity, or whether binding will cause any effect at all upon the assumed ability of the variant to promote or catalyze the polymerization of actin monomers within a cell, because it cannot be predicted whether these variants will have this or any other specific activity.

Applicant also argues that "variants will not include those that contain inactivating changes" (page 6, paragraph 3), because the claims require that the genus of PSTPIP-like polypeptides retain an ability to bind a protein tyrosine phosphatase. This argument is not found to be persuasive because, while the claims limit the scope of the invention to an antibody capable of specific binding to a PSTPIP-like polypeptide variant that

retains the ability to bind a protein tyrosine phosphatase, the specification is not enabling for the still broad scope of the claims, which encompass a multitude of PSTPIP variants that will not, nor would be expected to retain the ability to induce the polymerization of actin monomers. Again, the asserted utility of the PSTPIP-like polypeptide variants is to induce the polymerization of actin monomers. Applicant states that "one skilled in the art will recognize that a variant that retains specific functional attributes will function in substantially the same way as the species that was disclosed" (page 6, paragraph 3). However, this statement directly contradicts the teachings of Bowie, et al, Burgess, et al, and Lazar, et al, referenced in the 35 USC § 101 rejection of the Office Action, which indicate that one of skill in the art cannot predict whether a sequence variant of PSTPIP (SEQ ID NO: 1) will have the same ability to induce actin polymerization, as PSTPIP is purported to have, even if the variant retains the ability to bind a protein tyrosine phosphatase. Furthermore, it is noted that "binding" may result from specific, cross-specific, or non-specific interactions between the PSTPIP-like molecule and a protein tyrosine phosphatase; yet, the specification does not address this issue. Also, there are no indications in the claims that identify the domain of the protein tyrosine phosphatase to which the PSTPIP-like molecule must bind. Certainly there are a number of different types of protein domains that mediate binding to other proteins, which are well known in the art. It is conceivable that a PSTPIP-like polypeptide variant may bind to a protein tyrosine phosphatase but not act as a substrate for the phosphatase, because the variant may bind a domain that is not associated with the active site of the phosphatase. Furthermore, it is noted that there are a large number of protein tyrosine phosphatases, also well known in the art, to which the PSTPIP-like polypeptide might bind and which have very different biological functions. Certainly not all of the protein tyrosine phosphatases to which a variant of PSTPIP might bind are involved in actin polymerization and therefore some of the variants may not be useful. Therefore, it has been established that the scope of the claims is considerably more broad than the specification is enabling.

In the Office Action, the examiner stated that the asserted utility of the claimed genus of antibodies in an assay to measure cell proliferation is non-specific and

unsubstantial because antibodies to unrelated proteins that are expressed in proliferating cells can be used in these assays. Applicant argues that the examiner's position is untenable because "it is not the case that simply because one 'useful' way of doing a particular thing is already known, any other way is inherently not useful" (page 6, paragraph 4). It is not a question as to whether the claimed antibody is "useful", *per se*; it is a question as to whether there is a *specific and substantial asserted utility* for the claimed antibody. In the instant case, the standard that is applied in determining whether an invention is supported by a specific and substantial utility is not a measure of the "usefulness" of the claimed antibody, because there is a presumption that there is a use for the antibody in an assay for measuring cell proliferation; however, the standard that is applied is a measure of the novelty and substance of the asserted utility. Because any antibody to any protein that is expressed in proliferating cells can be used to mark proliferating cells and because the examiner cited an example of such, the asserted use of the claimed antibody capable of specific binding to PSTPIP is considered generic and therefore lacks specificity. Because it is well known by one skilled in the art that an antibody capable of binding a protein that is expressed in proliferating cells can be used to mark those cells and because there are numerous antibodies that can be used in these assays, the asserted utility for the claimed antibody is not considered to be substantial, since the contribution to the art is expected to be small in view of the pre-existing knowledge held in the art. Nonetheless, it is clear that one of skill in the art cannot predict whether each antibody encompassed by the claims, which is capable of specific binding to an individual member of the genus of PSTPIP-like polypeptide variants, will be useful in an assay to mark proliferating cells, because it cannot be predicted whether the PSTPIP-like molecule to which the antibody binds will be expressed in a cell cycle-dependent manner and would therefore be useful in marking a proliferating cell.

In view of the above, the arguments are not found to be persuasive and the rejection in section 8 of the Office Action is maintained. Because one cannot predict whether a PSTPIP-like polypeptide variant will have the ability to induce actin polymerization or that it will be expressed in a cell cycle-dependent manner, and

therefore an antibody capable of specific binding to the variant is not supported by a specific asserted utility, one skilled in the art clearly would not know how to use the claimed invention drawn to the full breadth of the claims.

With regard to the 35 USC § 112, first paragraph rejection of claim 22 in section 10 of the Office Action mailed on November 7, 2000, Applicant argues that the examiner's conclusion is unfounded and that "it is irrelevant whether or not the exact physiological mechanisms are understood" (page 7, paragraph 5). Also, Applicant states that the ability of the candidate antibody to act as an agonist or an antagonist "does not depend on the ability of PSTPIP to stimulate active polymerization in isolation" (page 8, paragraph 1). If these statements are true, where in the specification does Applicant teach what other components are required in the claimed assay for identifying an antagonist or agonist antibody of a PSTPIP polypeptide? It is implicit from the claim language that a candidate agonist or antagonist, actin monomers, and PSTPIP must be present in the assay, however, it cannot be ascertained what other components are required to monitor the ability of PSTPIP to induce actin polymerization; and yet, Applicant clearly indicates that the induction of actin polymerization does not depend upon the isolated activity of PSTPIP. On the other hand, since it has yet to be established that a variant of PSTPIP is capable of inducing actin polymerization, certainly one of skill in the art cannot use such a potentially inactive PSTPIP-like molecule, which is clearly encompassed by scope of the claim, in the assay with a reasonable expectation of success.

Also, Applicant states that "one skilled in the art can observe a result of PSTPIP overexpression, actin polymerization, as described in the specification" (page 7, paragraph 5). In this latter argument, it is noted that the features upon which Applicant relies (i.e., over-expression of PSTPIP) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

In the Office Action, the examiner stated that "in order to practice the invention as claimed, the integrity of a cell membrane would necessarily have to be disrupted in

order to contact PSTPIP with an antibody; and one would not expect PSTPIP to function normally in a disrupted, non-viable cell" (page 12, paragraph 2). Applicant submits that "a number of methods were known for conferring membrane permeability to otherwise impermeable proteins at the time the application was filed" (page 8, paragraph 2). However, it is noted that none of the references cited by the Applicant teach a method of conferring membrane permeability to an antibody capable of specific binding to PSTPIP which can act as either an agonist or an antagonist of the ability of PSTPIP to induce actin polymerization. Regardless of this fact, it is noted that that the features upon which Applicant relies (i.e., method steps that confer membrane permeability to otherwise impermeable proteins) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Also, if one were to have to resort to such methods to use the invention as claimed, then clearly Applicant would have had to refer to these methods in the specification. Applicant argues that "the specification provides sufficient detail to allow one of ordinary skill in the art to determine if a candidate antibody is an antagonist or agonist"; however, there are no such disclosures found in the specification. With regard to each of the methods that Applicant argues could have been used to confer membrane permeability to the antibody for use in the claimed assay, it is noted that one of skill in the art would not have been unable to practice the invention with a reasonable expectation of success. In the absence of sufficient guidance and exemplification, one would be forced into undue experimentation to practice the claimed invention.

In response to section 11 of the Office Action, Applicant has amended claims 15 and 22 to recite "followed by wash at 42°C" in lines 14-15 and to remove the term "substantially". The phrase "followed by wash" is indefinite because it cannot be determined how many washes are to be performed or for what length of time the washes are to be performed. Would a single wash step at 42°C in 0.2 x SSC and 0.1% SDS be sufficient to remove non-specific hybrids, especially if the wash was performed quickly? As such, it is still conceivable that a whole universe of complementary nucleic

acid molecules would hybridize, many of which would not have any structural or functional similarity to PSTPIP, and some of those which would encode polypeptides that are able to bind to a protein tyrosine kinase. Despite the fact that claims 1 and 22 indicate that stringent conditions are to be used, it is noted that the wash conditions recited in the claims are not highly stringent, as evidenced by the specification. On page 14, the specification defines a high-stringency wash as consisting of "0.1 x SSC containing EDTA at 55°C" (line 1-2). It is expected that since the conditions are not highly stringent, numerous unrelated polynucleotides will hybridize to the complement of SEQ ID NO: 2.

In regard to section 12 of the Office Action, Applicant states that the 35 USC § 112, first paragraph rejection of claims 15-18 and 22 should be withdrawn because the disclosure of two species of molecules within the genus of PSTPIP-like molecules is sufficiently descriptive of the genus (page 10, paragraph 4). However, it is noted that as the claims are written the scope of the invention encompasses an antibody that binds to a PSTPIP polypeptide variant that retains the ability to bind a protein tyrosine phosphatase and which does not have the ability to induce the polymerization of actin monomers. Clearly, since Applicant purports that both mouse and human homologues of PSTPIP function to induce actin polymerization, there is no disclosure of a species within the claimed genus of PSTPIP-like polypeptide variants that does not have the ability to induce polymerization, and therefore Applicant does not have a representative number of species. Nonetheless, Applicant contends that "whether a representative number of species is disclosed depends on whether one of skill in the art would recognize that Applicants were in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed or claimed" (pages 10-11). Applicant also states that "the genus must possess the functional ability to bind a protein tyrosine phosphatase" (page 11, paragraph 2). However, this contention seems to contradict the findings of the court (see *The Regents of the University of California v. Eli Lilly*, 43 USPQ2d 1398-1412), which upheld that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus.

Nevertheless, it is noted that the features upon which applicant relies (i.e., SEQ ID NO: 28 and 29) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Furthermore, while the Applicant states that "two species that are within the scope of the genus have been disclosed and reduced to practice" (page 10, paragraph 4), it is unclear to the examiner where in the specification the Applicant teaches the use of the PSTPIP variant having the amino acid sequence set forth in SEQ ID NO: 28. The examples in the specification appear to only teach the use of SEQ ID NO: 1.

Applicant also states that "the stringent hybridization conditions will yield insubstantial variation among the species within the genus" (page 11, paragraph 2). However, if mouse and human homologues are truly representative of the genus, as Applicant has suggested, because mouse and human sequences are not identical and it cannot be predicted whether mouse and human homologues of PSTPIP will function identically, based upon the teachings of Lazar, et al and Burgess, et al (cited in the Office Action), then what does Applicant consider insubstantial variation? Actually, the specification does not teach that human PSTPIP (SEQ ID NO: 28) has the ability to bind a protein tyrosine phosphatase or that it is able to induce actin polymerization. It is, however, required that the claimed antibody be capable of specific binding to a species of the genus of PSTPIP-like polypeptides that retains the ability to bind a protein tyrosine phosphatase, but it is not required that the PSTPIP-like polypeptide variant retain the ability to induce actin polymerization. The specification does not teach how one of skill in the art can use an antibody that specifically binds a PSTPIP-like polypeptide variant that does not induce actin polymerization. As such, one of skill in the art cannot use the invention to the full breadth of the claims without undue experimentation.

Additionally, it is noted that arguments set forth in paragraph 3 on page 10 and those set forth in paragraph 2 on page 11 are contradictory. The former argument states that "the claims at issue are not limited to polynucleotides". On the other hand,

the latter argument states that "the genus is restricted to those polynucleotides with specific structural and functional features".

***Second Paragraph***

11. Claims 15 and 22 have been amended to remove the term "substantially"; therefore, this rejection is withdrawn.

***Claim Rejections - 35 USC § 102***

12. Applicant's arguments filed January 29, 2001 have been fully considered but are not found to be persuasive and these rejections are maintained.

Claim 15 has been amended to recite the phrase "a polypeptide epitope of" in lines 1-2 so that now the claim reads on "an antibody capable of specific binding to a polypeptide epitope of a PST phosphatase interacting protein (PSTPIP) polypeptide consisting of a polypeptide comprising the amino acid sequence of the PSTPIP polypeptide shown in SEQ ID NO: 1. As indicated below, the amendment of claim 15 to include the phrase "polypeptide epitope" is not supported by the originally filed disclosure and is accordingly considered new matter. Nonetheless, Applicant's arguments are still considered.

Applicant argues that the prior art antibody of Sodhi, et al "the antibodies taught by Sodhi, et al will not always recognize PSTPIP proteins" (page 11, paragraph 5). However, it is noted that the features (i.e., conditional binding of the antibody) upon which applicant relies upon as a basis of argument are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Applicant states that the prior art antibody "will only recognize PSTPIPs if they contain a phosphorylated tyrosine residue" (page 11, paragraph 5). Essentially, claim 15 is drawn to an antibody capable of specific binding to a polypeptide comprising the amino acid sequence set forth in SEQ ID NO: 1. Clearly, the antibody of Sodhi, et al binds the polypeptide comprising the amino acid sequence set forth in SEQ ID NO: 1,

as Applicant admits, therefore, the prior art anticipates the claim. However, Applicant argues that "the antibodies of claim 15 [now amended] are not directed to a single amino acid residue or a specific post-translationally modified amino acid residue" (page 12, paragraph 1). Applicant further argues that the prior art antibody of Sodhi, et al binds "only a phosphorylated tyrosine residue and not a polypeptide epitope" (page 12, paragraph 1), as required by the now amended claim. The examiner disagrees with this statement. The phrase "polypeptide epitope" is not defined in the specification and the amendment of claim 15 to include the phrase necessitates the rejection of the claim under 35 USC § 112, first paragraph, because the phrase is considered new matter (see New Rejections). However, it is well known in the art that an epitope is the "determinant" of specific binding on a polypeptide sequence that is recognized by an antibody (see also page 11, line 38 within the specification). Accordingly, an epitope may well be a phosphorylated tyrosine residue contained within the polypeptide sequence of an antigen to which the antibody specifically binds. Therefore, for the purpose of weighing Applicant's arguments in view of the amended claim, it is reasonable to define a "polypeptide epitope" as an epitope contained in or present on the structure of a polypeptide to which an antibody specifically binds upon recognition of said epitope. Thus, the amendment to claim 15 has not effectively altered the scope of the original claim. Moreover, the specification teaches that an anti-phosphotyrosine antibody, such as the prior art antibody of Sodhi, et al, is capable of specific binding to a polypeptide epitope of a polypeptide comprising the amino acid sequence set forth in SEQ ID NO: 1, as evidenced, for example, by the description of Figure 6 (pages 4-5). As such, the prior art antibody of Sodhi, et al clearly anticipates the claims and the rejection in section 16 of the Office Action is maintained.

Applicant argues, with regard to the rejection in section 17 of the Office Action, that the prior art antibody will not always bind a PSTPIP protein and that "the antibodies taught by Frackleton, et al are not specific for a polypeptide epitope from a PSTPIP polypeptide" (page 12, paragraphs 3-4). Again, it is noted that the features (i.e., conditional binding of the antibody) upon which applicant relies upon as a basis of argument are not recited in the rejected claim(s). Although the claims are interpreted in

light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). As to the statement that the prior art antibodies of Frackleton, et al do not bind specifically to a polypeptide epitope, this argument is simply not true. The polypeptide epitope comprising the phosphorylated tyrosine residue of a polypeptide comprising the amino acid sequence set forth in SEQ ID NO: 1 is specifically recognized and bound by the prior art antibody, as evidenced by the teachings of the specification (see, for example, Figure 6), and thus clearly anticipate the claims.

With regard to the rejection in section 18 of the prior Office Action, Applicant argues that "anti-FLAG antibodies would not react with PSTPIP polypeptides and clearly do not anticipate the instant claims" (page 13, paragraph 2). Applicant further argues that "as the sequence of the FLAG polypeptide differs from the sequence of the PSTPIPs, the PSTPIPs will not contain epitopes that are recognized by anti-FLAG antibodies" (page 13, paragraph 2). Applicant then argues that "the fact that antibodies are known that recognize polypeptides with could be incorporated in a chimeric protein with PSTPIP is irrelevant" and "the present claims are not drawn to such molecules" (page 13, paragraph 2).

Because open language, as opposed to closed language, is used in claim 15 (i.e., the use of *comprising* terminology rather than, for example, *consisting of* terminology), the claims encompass an antibody that is capable of specific binding to a polypeptide, which includes, but is not limited to the amino acid sequence set forth in SEQ ID NO: 1. Therefore, an antibody capable of specific binding to a fusion protein comprising PSTPIP (SEQ ID NO: 1) and another polypeptide (e.g. a FLAG-epitope tag) is reasonably considered to fall within the scope of claimed invention.

The prior art antibody of Su, et al clearly anticipates the claims, because the prior art antibody is capable of specific binding to a polypeptide comprising the amino acid sequence set forth in SEQ ID NO: 1. It is irrelevant that the polypeptide to which the antibody specifically binds comprises an amino acid sequence other than the amino acid sequence set forth in SEQ ID NO: 1, because the claims encompass antibodies capable of specific binding to a polypeptide comprising the sequence set forth in SEQ

ID NO: 1 and any other sequence. In fact, the specification teaches an anti-FLAG antibody (i.e., the prior art antibody of Su, et al) is, in fact, capable of specific binding to a polypeptide comprising the amino acid sequence set forth in SEQ ID NO: 1 and the amino acid sequence designated the FLAG-epitope tag (see, for example, the description of Figure 6, pages 4-5).

In regard to section 19 of the prior Office Action, a prior art rejection was made on the basis that claim 15 is anticipated by Parthun, et al. Parthun, et al teach antibodies that are capable of binding GAL4 protein. The polynucleotide sequence set forth in SEQ ID NO: 2 comprises a polynucleotide sequence that encodes the GAL4 protein to which the prior art antibody of Parthun, et al is known to specifically bind. Applicant argues that the rejection should be withdrawn because "the nucleotide sequence identity between GAL4 and PSTPIP corresponds only to 5'-untranslated PSTPIP sequence" (page 14, paragraph 3). Applicant also argues that "because the area of homology is in an area that is not translated, the GAL4 gene does not encode a protein that is identical to any part of the amino acid sequence of SEQ ID NO: 1" and "as a result, the prior art antibody will not be capable of specifically binding a polypeptide epitope as claimed" (page 14, paragraph 1).

There is no evidence in the record that the nucleotide sequence of SEQ ID NO: 2 encoding the GAL4 protein is contained within the 5'-untranslated region of the polynucleotide encoding the PSTPIP polypeptide comprising the amino acid sequence identified in SEQ ID NO: 1. Furthermore, there is no evidence in the record that the nucleotide sequence of SEQ ID NO: 2 encoding the GAL4 protein is not transcribed or that the mRNA transcript of SEQ ID NO: 2, if it does contain the nucleotide sequence encoding the GAL4 protein, is not translated to produce the GAL4 protein. Certainly, it is conceivable that there is more than one transcriptional start site present in the nucleic acid molecule comprising SEQ ID NO: 2, which will facilitate the expression of the nucleotide sequence encoding the GAL4 protein. It is also conceivable that the GAL4 protein is expressed as a fusion protein, which comprises the PSTPIP polypeptide. There is no evidence in the record that proves that a fusion protein comprising the GAL4 protein and the PSTPIP polypeptide is not expressed.

The examiner agrees with Applicant's statement that the GAL4 gene does not encode any part of the amino acid sequence of SEQ ID NO: 1; however, it is noted that the polynucleotide sequence set forth in SEQ ID NO: 2 does encode at least a portion of GAL4 protein, because SEQ ID NO: 2 is 100% identical to the sequence of the nucleic acid molecule encoding GAL4 over a span of 344 nucleotides. Furthermore, claim 15 is drawn to an antibody capable of specific binding to an epitope of a polypeptide encoded by a nucleic acid molecule that hybridizes under stringent conditions to the complement of the polynucleotide sequence set forth in SEQ ID NO: 2. Clearly, the nucleic acid molecule encoding the GAL4 protein will hybridize to the complement of the polynucleotide sequence set forth in SEQ ID NO: 2, because the sequence of the nucleic acid molecule encoding the GAL4 protein is identical to a portion SEQ ID NO: 2. Also, it is clear that the prior art antibody of Parthun, et al is capable of specific binding to the polypeptide that is encoded by this portion of SEQ ID NO: 2, because Parthun, et al teach that the antibody is capable of specific binding to a polypeptide encoded by an identical polynucleotide sequence. Provided that that there in not a shift in the reading frame of the coding sequences for the GAL4 protein and the PSTPIP polypeptide (SEQ ID NO: 1), expression of the polynucleotide sequence set forth in SEQ ID NO: 1 will produce a fusion protein that comprises both the amino acid sequences of the GAL4 protein and a PSTPIP polypeptide. Parthun, et al, anticipates the claim because the prior art antibody is certainly capable of specific binding to this fusion protein, which according to the teachings of the specification should retain the ability to bind to a protein tyrosine phosphatase. Because the specification does not identify the open reading frame of the polynucleotide sequence encoding PSTPIP or teach that there is a frame shift in the open reading frames encoding PSTPIP and the GAL4 protein, there is a reasonable presumption that the prior art antibody anticipates claim 15.

As to the Applicant's argument that the coding sequence of the GAL4 protein is contained in the 5'-untranslated region of SEQ ID NO: 2, it is noted that the features upon which applicant relies (i.e., a polypeptide encoded by a nucleic acid molecule that hybridizes under stringent conditions to the complement of the polynucleotide sequence set forth in *a particularly defined open reading frame* of SEQ ID NO: 2) are not recited in

the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Therefore, Applicant's arguments are not found to be persuasive and the rejections are maintained.

***Claim Rejections - 35 USC § 103***

13. Applicant's arguments filed January 29, 2001 have been fully considered but are not found to be persuasive and this rejection is maintained.

In section 21 of the prior Office Action claim 15 was rejected as being unpatentable over the prior art. Applicant argues that Bennett, et al disclose the same sequence as that in the Parthun, et al rejection. Applicant states that "there is no homology at the amino acid level" between GAL4 and PSTPIP and "anti-GAL4 antibodies would not recognize any epitopes on PSTPIP polypeptides" (page 14, paragraph 3). Applicant reiterates these arguments with respect to the rejection made in section 22 of the prior Office Action over Green Cross Corp. It is noted that Applicant does not refute the grounds of these rejections otherwise.

These arguments are not found to be persuasive for the reasons set forth above. Again, there is no evidence in the record that the nucleotide sequence of SEQ ID NO: 2 encoding the GAL4 protein is contained within the 5'-untranslated region of the polynucleotide encoding the PSTPIP polypeptide comprising the amino acid sequence identified in SEQ ID NO: 1 or that the GAL4 protein is not expressed as a fusion protein further comprising the PSTPIP polypeptide. Accordingly, there is a reasonable presumption that the polynucleotide sequence set forth in SEQ ID NO: 2 encodes a fusion protein comprising both the amino acid sequences of the GAL4 protein and a PSTPIP polypeptide.

***New Claim Rejections – 35 USC § 112***

14. Claims 15-18 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to

reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to an antibody capable of specific binding to a PSTPIP. Claim 15 has been amended to include the phrase "a polypeptide epitope of" in lines 1-2 to overcome a 35 USC § 102(b) rejection that was made in the previous Office Action. However, there appears to be no support for the phrase "polypeptide epitope" in the specification; most notably, support was not identified on page 29, lines 27-34, where Applicant contends support can be found. Therefore, the amendment is considered to introduce new matter into the claims. In addition, 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention.

15. Claims 15-18 and 22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an antibody capable of specific binding to PSTPIP comprising a polypeptide comprising the amino acid sequence set forth in SEQ ID NO: 1, does not reasonably provide enablement for an antibody capable of specific binding to PSTPIP comprising a polypeptide encoded by a nucleic acid which hybridizes under stringent conditions to the complement of nucleic acid of SEQ ID NO: 2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claims are drawn to an antibody and an assay for identifying an agonist or an antagonist antibody. Claims 15 and 22 were amended to include the phrase "followed by wash at 42°C" in lines 14-15 to overcome a 35 USC § 112, first paragraph rejection that was made in the previous Office Action. The amendment is not sufficient to overcome the rejection made previously, as indicated above. However, the amendment necessitates new grounds for rejection, because the teachings of the specification cannot be extrapolated to the scope of the claims. It is noted that the conditions for the wash are not highly stringent, as evidenced by the teachings of the specification (page 14, lines 1-2). Moreover, the amended claims do not recite the number of times or for what duration of time the wash step should be performed.

According to the claims, in the absence of any teaching in the specification, the wash time could be overly brief; clearly a short wash time will be less effective at removing non-specific or poorly hybridizing molecules. Therefore, it is anticipated that a whole universe of polypeptides will hybridize the complement of a polynucleotide sequence of SEQ ID NO: 2 that retain the ability to bind to a protein tyrosine phosphatase but will not induce the polymerization of actin monomers. Neither the claims nor the specification teach how an antibody capable of specific binding to a PSTPIP-like polypeptide variant that retains the ability to bind to a protein tyrosine kinase, but which does not have the ability to induce the polymerization of actin monomers. For this reason, one of skill in the art cannot practice the invention drawn to the breadth of the claims with a reasonable expectation of success without undue experimentation.

16. Claims 15-18 and 22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are indefinite because claims 15 and 22 recite the phrase "followed by wash at 42°C". The phrase "followed by wash at 42°C" is indefinite because it cannot be ascertained how many times or for what duration of time wash is to be performed. Neither the preamble of the claims nor the specification provides a disclosure as to how many times or for what duration of time the wash step is required to be performed. Furthermore, because the number of molecules that would be expected to hybridize the complement of SEQ ID NO: 2 is highly variable depending upon the conditions and number of the wash steps, the scope of the claims cannot be determined.

***Conclusion***

17. No claims are allowed.

18. Applicant's amendment of the claims necessitated the new ground(s) of rejection presented in this Office Action. Accordingly, **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

19. Without affirming its patentability, it is suggested that an application that claims an antibody that binds specifically to a PSTPIP polypeptide consisting of the amino acid sequence set forth in SEQ ID NO: 1 may receive more favorable consideration by the Office.

Without affirming its patentability, it is suggested that an application that claims an assay for identifying a cell membrane permeable agonist or antagonist antibody that binds specifically to a PSTPIP polypeptide consisting of the amino acid sequence set forth in SEQ ID NO: 1, wherein binding of said antibody stimulates or inhibits the polymerization of actin monomers induced by over-expression of the PSTPIP polypeptide within a cell, comprising contacting said antibody to said PSTPIP polypeptide, detecting an increase or decrease in the level of actin polymerization, and correlating the detected level with the presence or absence of the antibody, whereby an agonist antibody is identified if there is an increase in the level of actin polymerization and an antagonist antibody is identified if there is a decrease in the level of actin polymerization.

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is

(703) 305-3008. The examiner can normally be reached on Monday-Thursday, alternate Fridays, 8:00AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony C. Caputa, Ph.D. can be reached on (703) 308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Stephen L. Rawlings, Ph.D.
Art Unit 1642

DONNA WORTMAN
PRIMARY EXAMINER

slr
March 19, 2001

| Notice to Comply | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/068,377 | LASKY ET AL. | |
| | Examiner | Art Unit | |
| | Stephen L. Rawlings, Ph.D. | 1642 | |

## NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☐ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☒ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☐ 7. Other:

### Applicant Must Provide:

☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☐ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

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